

Date: February 4, 2021

Submitted electronically at www.regulations.gov to Docket EPA-HQ-OPP-2008-0850

Re: December 2020 [Proposed Interim Decision for the Registration Review of Chlorpyrifos](#)

Scientific Letter on Chlorpyrifos and Neurodevelopmental Harm

To the EPA Pesticide Office,

We are scientists and health professionals with expertise in toxic chemicals that harm the developing brain. Many of us are affiliated with Project TENDR, a collaboration of leading scientists, health professionals, and children's health and environmental advocates who have come together out of concern over the substantial evidence linking toxic chemicals to neurodevelopmental disorders, such as autism spectrum disorder, attention deficits, hyperactivity, intellectual disability, and learning disorders.¹

In 2016, Project TENDR published a consensus statement that reviewed the scientific evidence and identified organophosphate pesticides, chlorpyrifos among them, as prime examples of chemicals that contribute to intellectual impairment and to a suite of neurodevelopmental disorders in America's children.² For that reason, in 2018 many of us co-authored a scientific review of the health harms posed by organophosphate pesticide exposures and made policy recommendations to protect pregnant women and children.³ That article concluded that, "Compelling evidence indicates that prenatal exposure at low levels is putting children at risk for cognitive and behavioral deficits and for neurodevelopmental disorders."⁴ We refer readers to that publication for details of the scientific evidence, and here provide a summary.

Organophosphate compounds encompass a class of several dozen insecticides and other chemicals. Sarin, the chemical warfare agent used in the Tokyo subway attacks is a member of the organophosphate family. Organophosphate insecticides are used to control a wide range of insects, and they are extremely toxic to the human brain and nervous system. Children are especially vulnerable, and this vulnerability is greatest during the nine months of pregnancy and in the first years after birth when children's brains are rapidly growing and developing. When a pregnant woman is exposed to chlorpyrifos, the chemical moves quickly through her bloodstream and into the blood flowing to the fetus. Chlorpyrifos can then disrupt the development of the brain. Studies conducted worldwide have linked low and transient prenatal organophosphate pesticide exposures in diverse populations across both urban and agricultural settings with decreased IQ scores and impaired cognitive, behavioral, and

¹ For additional information on Project TENDR, see <http://projecttendr.com>.

² Bennett D, Bellinger DC, Birnbaum LS, Bradman A, Chen A, Cory-Slechta DA, et al. Project TENDR: Targeting Environmental Neuro-Developmental Risks The TENDR Consensus Statement. *Environ Health Perspect*. 2016; 124(7):A118–22. <https://doi.org/10.1289/EHP358>.

³ Hertz-Picciotto I, Sass JB, Engel S, Bennett DH, Bradman A, Eskenazi B, Lanphear B, Whyatt R. Organophosphate exposures during pregnancy and child neurodevelopment: Recommendations for essential policy reforms. *PLoS Med*. 2018 Oct 24;15(10):e1002671. doi: 10.1371/journal.pmed.1002671. PMID: 30356230; PMCID: PMC6200179

⁴ Hertz-Picciotto I, Sass JB, Engel S, Bennett DH, Bradman A, Eskenazi B, Lanphear B, Whyatt R. Organophosphate exposures during pregnancy and child neurodevelopment: Recommendations for essential policy reforms. *PLoS Med*. 2018 Oct 24;15(10):e1002671. doi: 10.1371/journal.pmed.1002671. PMID: 30356230; PMCID: PMC6200179

social development in children.⁵ Because the human brain has little capacity to repair itself, brain injury caused by organophosphate exposure in early life can lead to permanent, lifelong impairment.

Importantly, the neurodevelopmental toxicity of chlorpyrifos occurs at levels of exposure well below those that cause acute poisoning or inhibition of the enzyme, acetylcholinesterase (“AChE”).⁶ AChE inhibition, which is measured in a blood test, is a widely used measure of organophosphate exposure and toxicity. Indeed, the scientific consensus is that AChE inhibition is uninformative with regard to neurodevelopmental effects in prenatally exposed children. Multiple, high-quality studies have shown that the developmental effects from low-level exposures to organophosphate pesticides, like chlorpyrifos, occur at concentrations too low to inhibit AChE by even as little as 10%.⁷ The US EPA acknowledged this shortcoming in the AChE assay in their 2015 literature review of organophosphate pesticides,⁸ as well as in the Agency’s 2014⁹ and 2016¹⁰ human health risk assessments for chlorpyrifos. Most recently, the EPA concluded that the existing epidemiologic literature provides “sufficient evidence that there are neurodevelopmental effects occurring at chlorpyrifos exposure levels below those required to cause acetylcholinesterase inhibition.”¹¹

The weight-of-evidence thus indicates that chlorpyrifos can interfere with brain development at levels below those that cause AChE inhibition. This means that a benchmark dose based on 10% inhibition of AChE does not provide an exposure threshold sufficient to ensure prevention of damage to the developing brain. **Hence, AChE inhibition is an under-protective biomarker. Reliance on AChE inhibition for regulatory purposes obscures the serious threat that chlorpyrifos poses to early brain development and represents an insensitive, unscientific and inadequate approach to health risk assessment.**

⁵ Gonzalez-Alzaga B, Lacasana M, Aguilar-Garduno C, Rodriguez-Barranco M, Ballester F, Rebagliato M, et al. A systematic review of neurodevelopmental effects of prenatal and postnatal organophosphate pesticide exposure. *Toxicol Lett.* 2014; 230(2):104–21. <https://doi.org/10.1016/j.toxlet.2013.11.019>; Koureas M, Tsakalof A, Tsatsakis A, Hadjichristodoulou C. Systematic review of biomonitoring studies to determine the association between exposure to organophosphorus and pyrethroid insecticides and human health outcomes. *Toxicol Lett.* 2012; 210(2):155–68. <https://doi.org/10.1016/j.toxlet.2011.10.007>; Munoz-Quezada MT, Lucero BA, Barr DB, Steenland K, Levy K, Ryan PB, et al. Neurodevelopmental effects in children associated with exposure to organophosphate pesticides: a systematic review. *Neurotoxicology.* 2013; 39:158–68. <https://doi.org/10.1016/j.neuro.2013.09.003>.

⁶ U.S. EPA. Chlorpyrifos: Revised Human Health Risk Assessment for Registration Review. US Environmental Protection Agency Washington, DC; 2016. Document ID: EPA-HQ-2015-0653-0454. Available from: <https://www.regulations.gov/document?D=EPA-HQ-OPP-2015-0653-0454>.

⁷ Costa LG. Organophosphorus Compounds at 80: Some Old and New Issues. *Toxicol Sci.* 2018;162(1):24–35. Epub 2017/12/12. pmid:29228398; Munoz-Quezada MT, Lucero BA, Barr DB, Steenland K, Levy K, Ryan PB, et al. Neurodevelopmental effects in children associated with exposure to organophosphate pesticides: a systematic review. *Neurotoxicology.* 2013;39:158–68. pmid:24121005; PubMed Central PMCID: PMC3899350.

⁸ EPA OPP, Literature Review on Neurodevelopmental Effects & FQPA Safety Factor Determination for the Organophosphate Pesticides (Sept. 15, 2015), at <http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2010-0119-0023>.

⁹ US EPA, 2014. Chlorpyrifos: Revised Human Health Risk Assessment for Registration Review. Available at: <http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2008-0850-0195>.

¹⁰ U.S. EPA. Chlorpyrifos: Revised Human Health Risk Assessment for Registration Review. US Environmental Protection Agency Washington, DC; 2016. Document ID: EPA-HQ-2015-0653-0454. Available from: <https://www.regulations.gov/document?D=EPA-HQ-OPP-2015-0653-0454>.

¹¹ *Id.*

It is important to note that in addition to being exquisitely sensitive to harm from exposure to organophosphates like chlorpyrifos, infants and young children are also commonly exposed to this insecticide. Due to their small body size and greater intake of food per pound of body weight, EPA estimates that children ages 1 to 12 are exposed to significantly more chlorpyrifos per pound of body weight through their diets than adults. Further, chlorpyrifos is authorized for use on nearly 50 food crops, including fruits, vegetables, and nuts heavily consumed by children. In annual tests for pesticide residues on conventionally grown produce, the U.S. Department of Agriculture finds chlorpyrifos on several commonly eaten fruits and vegetables, with especially high concentrations on soft-skinned fruits and some leafy greens. Residues are also common in several imported foods at levels much higher than in corresponding, domestically grown foods.¹²

Continued exposure to chlorpyrifos in pregnant women and children, coupled with exquisite sensitivity to toxic brain injury during fetal and early life development underscores the need for EPA to rely on neurodevelopmental harm in its human health risk assessment and to set exposure standards at levels low enough to prevent brain injury in infants and children. Chlorpyrifos' capacity to disrupt neurological development should be the basis for determining whether existing chlorpyrifos tolerances comply with the "reasonable certainty of no harm" standard in the FQPA. We conclude they do not.

Sincerely,

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¹² Benbrook, C and Davis D. "The dietary risk index system: a tool to track pesticide dietary risks;" Environmental Health, 2020, 19(1); DOI: 10.1186/s12940-020-00657-z.

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